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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/070,240	02/27/2002	Takuya Watanabe	57127 (46342)	2962

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EXAMINER	
BUNNER, BRIDGET E	
ART UNIT	**PAPER NUMBER**
1647	

DATE MAILED: 11/04/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/070,240	WATANABE ET AL.	
	Examiner	Art Unit	
	Bridget E. Bunner	1647	

-- The MAILING DATE of this communication app ars on the cover sheet with the correspond nce address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 September 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14* is/are pending in the application.

4a) Of the above claim(s) *3-8,10 and 12-14* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,9 and 11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-14* are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *2/27/2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *2/27/02* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Status of Application, Amendments and/or Claims

The amendment of 27 February 2002 and 09 August 2002 have been entered in full.

Election/Restrictions

Applicant's election of Group I, claims 1-2, 9, and 11 in the paper of 15 September 2003 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 3-8, 10, and 12-14 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected group, there being no allowable generic or linking claim. Election was made **without** traverse in the paper of 15 September 2003.

Claims 1-2, 9, and 11 are under consideration in the instant application.

Claim Rejections - 35 USC § 101 and 35 U.S.C. § 112, first paragraph

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

1. Claims 1-2, 9, and 11 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. Claims read on a product of nature in that the claimed peptides are not "isolated". In the absence of the hand of man, the naturally occurring products are considered non-statutory subject matter. *See Diamond v. Chakrabarty*, 447 U.S. 303, 206

USPQ 193 (1980). The claims should be amended to indicate the hand of the inventor, e.g., by insertion of "isolated" or "purified" as taught by pages 76-80 of the specification. See MPEP 2105.

2. Claim 9 is rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

3. Claims 1-2, 9, and 11 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a credible, specific and substantial asserted utility or a well established utility. Novel biological molecules lack well established utility and must undergo extensive experimentation.

Specifically, the claims are directed to a protein which comprises the same or substantially the same amino acid sequence as the amino acid sequence represented by SEQ ID NO: 1, or a salt thereof. The claims recite a partial peptide of the protein according to claim 1, or a salt thereof. The claims recite a method of determining a ligand to the protein or its salt, which comprises using the protein or the partial peptide, or a salt thereof. The claims also recite a kit for screening a compound or its salt that alters the binding property between a ligand and the protein comprising the protein or the partial peptide or a salt thereof.

The specification asserts that the human brain-derived protein (SEQ ID NO:1) and DNA encoding the protein (SEQ ID NO: 2) of the present invention represent a novel G protein-coupled receptor (pg 1, lines 23-24; pg 2, lines 29-30). The specification also discloses that the

G protein-coupled receptor plays important physiological roles as the targets of molecules that regulate the functions of the cells and organs, e.g., hormones, neurotransmitters, physiologically active substances and the like (pg 1, lines 23-28). However, the instant specification does not teach any significance or functional characteristics of the polynucleotide (SEQ ID NO: 2) or protein (SEQ ID NO: 1). The specification also does not disclose any methods or working examples that indicate the polynucleotide and protein of the instant invention are involved in any activities. Since significant further research would be required of the skilled artisan to determine how the claimed protein is involved in any activity, the asserted utilities are not substantial. Since the utility is not presented in mature form and significant further research is required, the utility is not substantial. The specification asserts the following as patentable utilities for the claimed putative protein (SEQ ID NO: 1):

1) to produce antibodies against the protein (pg 34-38)

2) to determine the ligand to the protein (pg 38, lines 26-38 through pg 47, lines 1-23)

3) to treat diseases associated with dysfunction of the claimed protein (pg 47, lines 25-38 through pg 51, lines 1-10)

4) to screen for compounds that alter the binding between the ligand and protein (pg 52-64)

Each of these shall be addressed in turn.

1) to produce antibodies against the protein. This asserted utility is not specific or substantial. Antibodies can be made to any protein. However, if the specification discloses nothing specific and substantial about the protein, therefore both protein and its antibodies have no patentable utility. Since this asserted utility is also not present in mature form so that it could be readily used in real world sense, the asserted utility is not substantial.

2) to determine the ligand to the protein. This asserted utility is not specific or substantial. Such assays can be performed with any protein. Nothing is disclosed about how the protein is affected by a ligand. Additionally, the specification discloses nothing specific or substantial for the possible ligands screened and identified in this method. Since this asserted utility is also not presented in mature form, so that it could be readily used in a real world sense, the asserted utility is not substantial.

Furthermore, it is noted that the specification teaches that ZAQ GPCR (SEQ ID NO: 1) activity is measured by observing increases of intracellular calcium concentrations with FLIPR (pg 80-83, 92-93, 97). However, relevant literature teaches that intracellular calcium is a universal second messenger that serves as a broad-based measure of receptor activity (Lin et al., Biotechniques 26: 318-326, 1999; abstract). G-protein coupled receptors appear to be *generalists* in their intracellular transduction cascades, and one would expect that an unknown receptor *would* likely generate an increase in intracellular calcium after receptor activation. The specification does not disclose any methods or working examples that indicate the protein of the instant invention is involved in any *specific* activities. Also, as mentioned above, the specification discloses nothing specific or substantial for the proteins or compounds utilized in the FLIPR assays. For example, it is not clear what substances or class of substances were used in the FLIPR screening assays.

3) to treat diseases associated with dysfunction of the claimed protein. This asserted utility is not specific or substantial. The specification does not disclose specific diseases or disorders associated with altered levels or forms of the protein of SEQ ID NO: 1. Significant further experimentation would be required of the skilled artisan to identify individuals with such

a disease. Since this asserted utility is also not present in mature form, so that it could be readily used in a real world sense, the asserted utility is not substantial.

4) to screen for compounds that alter the binding between the ligand and protein. This asserted utility is not specific or substantial. Such assays can be performed with any protein. Additionally, the specification discloses nothing specific or substantial for the compounds that can be identified by this method. Since this asserted utility is also not present in mature form, so that it could be readily used in a real world sense, the asserted utility is not substantial.

4. Claims 1-2, 9, and 11 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

5. Furthermore, claims 1-2, 9, and 11 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

As discussed above, the claims are directed to a protein which comprises the same or substantially the same amino acid sequence as the amino acid sequence represented by SEQ ID NO: 1, or a salt thereof. The claims recite a partial peptide of the protein according to claim 1, or a salt thereof. The claims recite a method of determining a ligand to the protein or its salt, which comprises using the protein or the partial peptide, or a salt thereof. The claims also recite a kit for screening a compound or its salt that alters the binding property between a ligand and the protein comprising the protein or the partial peptide or a salt thereof.

The specification teaches that "the substantially the same amino acid sequence includes an amino acid sequence having at least 50% homology, preferably at least about 70% homology, more preferably at least about 80% homology, much more preferably at least about 90% homology and most preferably at least about 95% homology to the amino acid sequence represented" (pg 15, lines 1-6). The specification also discloses that for the partial peptide of the protein of present invention, any partial peptide described for the protein can be used (pg 14, lines 19-22). The specification teaches that the partial peptide "is a peptide having at least 20, preferably at least 50 and more preferably at least 100 amino acids, in the amino acid sequence, which constitutes the protein of the present invention" (pg 14, lines 34-38). However, the specification does not teach any variants, homologs, or fragments of the brain derived protein of SEQ ID NO: 1. Additionally, the specification does not teach any specific functional or structural characteristics of any polynucleotide/protein variants, homologs, or fragments in the context of a cell or organism.

The problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein, the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These or other regions may also be critical determinants of antigenicity. These regions can tolerate only relatively conservative substitutions or no substitutions (see Wells, 1990, Biochemistry 29:8509-8517; Ngo et al., 1994,

The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495). However, Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions. Although the specification outlines art-recognized procedures for producing and screening for active muteins, this is not adequate guidance as to the nature of active derivatives that may be constructed, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. Even if an active or binding site were identified in the specification, they may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity. The art recognizes that function cannot be predicted from structure alone (Bork, 2000, Genome Research 10:398-400; Skolnick et al., 2000, Trends in Biotech. 18(1):34-39, especially p. 36 at Box 2; Doerks et al., 1998, Trends in Genetics 14:248-250; Smith et al., 1997, Nature Biotechnology 15:1222-1223; Brenner, 1999, Trends in Genetics 15:132-133; Bork et al., 1996, Trends in Genetics 12:425-427).

Due to the large quantity of experimentation necessary to generate the infinite number of derivatives recited in the claims and possibly screen same for activity, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims which fail to

recite any structural or functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

6. Claims 1-2, 9, and 11 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are directed to a protein which comprises the same or substantially the same amino acid sequence as the amino acid sequence represented by SEQ ID NO: 1, or a salt thereof. The claims recite a partial peptide of the protein according to claim 1, or a salt thereof. The claims recite a method of determining a ligand to the protein or its salt, which comprises using the protein or the partial peptide, or a salt thereof. The claims also recite a kit for screening a compound or its salt that alters the binding property between a ligand and the protein comprising the protein or the partial peptide or a salt thereof.

The specification teaches that "the substantially the same amino acid sequence includes an amino acid sequence having at least 50% homology, preferably at least about 70% homology, more preferably at least about 80% homology, much more preferably at least about 90% homology and most preferably at least about 95% homology to the amino acid sequence represented" (pg 15, lines 1-6). The specification also discloses that for the partial peptide of the protein of present invention, any partial peptide described for the protein can be used (pg 14, lines 19-22). The specification teaches that the partial peptide "is a peptide having at least 20, preferably at least 50 and more preferably at least 100 amino acids, in the amino acid sequence,

which constitutes the protein of the present invention" (pg 14, lines 34-38). However, the specification does not teach any specific functional or structural characteristics of the protein variants, homologs, or fragments in the context of a cell or organism. The description of one DNA species (SEQ ID NO: 2) and one protein species (SEQ ID NO: 1) is not adequate written description of an entire genus of functionally equivalent polypeptides which incorporate all variants, homologs, and fragments of the protein of SEQ ID NO: 1.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed"* (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed" (See *Vas-Cath* at page 1116).

With the exception of the sequences referred to above, the skilled artisan cannot envision the detailed chemical structure of the encompassed polynucleotides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The nucleic acid itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only an isolated protein consisting of the sequence of SEQ ID NO: 1, but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claim 9 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

8. Claim 9 provides for the use of a protein or partial peptide, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

9. Claim 9 is indefinite because the claim does not have a step that clearly relates back to the preamble. For example, there is no step indicating that a compound is identified that alters the binding property between a ligand and a protein.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. Claims 1-2, 9, and 11 are rejected under 35 U.S.C. 102(b) as being anticipated by Moore et al. (U.S. Patent 5,891,720).

Moore et al. teach a protein which comprises substantially the same amino acid sequence as the amino acid sequence represented by SEQ ID NO: 1 of the instant application (i.e., 85.9% identical; see sequence alignment attached to this Office Action as Appendix A; see also amino acids 3-284 of SEQ ID NO: 2 in Moore et al.). Moore et al. also teach a partial peptide of the protein represented by SEQ ID NO: 1 of the instant application (see sequence alignment attached to this Office Action as Appendix A; see also amino acids 3-284 of SEQ ID NO: 2 in Moore et al.). Moore et al. teach a method of determining a ligand to the protein comprising substantially the same amino acid sequence as SEQ ID NO: 1 of the instant application (col 23, lines 39-67; col 24, lines 1-67). Finally, Moore et al. teach a kit comprising the protein comprising substantially the same amino acid sequence as SEQ ID NO: 1 of the instant application or a partial peptide of the protein of SEQ ID NO:1 of the instant application (col 36, lines 1-67; col 37, lines 1-11).

Conclusion

No claims are allowable.

The art made of record and not relied upon is considered pertinent to applicant's disclosure:

Rcferences that disclose the entire or partial claimed protein sequence:

Masuda Y et al. Biochem Biophys Res Commun. 293(1): 396-402, 2002.
Soga T et al. Biochim Biophys Acta. 1579(2-3):173-179, 2002.
Parker R et al. Biochim Biophys Acta. 1491(1-3): 369-375, 2000.
Cheng et al. Nature. 417(6887):405-410, 2002.

References about FLIPR/intracellular Ca+ mobilization and GPCR:

Niedernberg et al. J Biomol Screen. 8(5):500-510, 2003.
Kassack et al. J Biomol Screen. 7(3):233-246, 2002.
Sullivan et al. Methods Mol Biol. 114:125-133, 1999.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bridget E. Bunner whose telephone number is (703) 305-7148. The examiner can normally be reached on 8:30-5:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on (703) 308-4623. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 872-9305.

BEB
Art Unit 1647
30 October 2003

Gary L. Kunz
GARY KUNZ
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